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Use of Bivalirudin During Percutaneous Coronary Intervention in Patients With Diabetes Mellitus

An Analysis From the Randomized Evaluation in Percutaneous Coronary Intervention Linking Angiomax to Reduced Clinical Events (REPLACE)-2 Trial

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OBJECTIVES The objective of this study was to confirm that the efficacy and safety of percutaneous coronary intervention (PCI) in diabetic patients are not compromised by a bivalirudin-based antithrombotic strategy.

BACKGROUND Previous studies have shown a survival benefit with use of platelet glycoprotein (GP) IIb/IIIa inhibitors in diabetic patients undergoing PCI. The Randomized Evaluation in Percutaneous Coronary Intervention Linking Angiomax to Reduced Clinical Events (REPLACE)-2 trial showed the non-inferiority of a strategy of bivalirudin with provisional GP IIb/IIIa inhibition compared with routine GP IIb/IIIa inhibition. The relative efficacy of these two strategies in diabetic patients has not been studied.

METHODS We evaluated the diabetic patients enrolled in the REPLACE-2 trial to assess the impact of these antithrombotic strategies on the short- and long-term outcome after PCI.

RESULTS The REPLACE-2 trial enrolled 1,624 diabetic patients and 4,368 non-diabetic patients. Compared with non-diabetic patients, diabetic patients had similar short-term outcome but higher mortality at 1 year (3.06% vs. 1.85%, $p = 0.004$). There was no difference in short-term or long-term ischemic events among the diabetic patients randomized to the two arms. Specifically, the 1-year mortality rate was non-significantly lower in the bivalirudin arm, suggesting no differential survival impact of the two strategies (2.3% vs. 3.9%). There was less minor bleeding in the bivalirudin arm in diabetic patients (12.6% vs. 24.4%, $p < 0.001$), whereas no difference was seen in the incidence of major bleeding (3.0% vs. 3.3%, $p = 0.69$).

CONCLUSIONS Compared with routine GP IIb/IIIa inhibition, the use of bivalirudin with provisional GP IIb/IIIa inhibitors in diabetic patients is associated with no differences in clinical outcomes at 30 days, a trend toward lesser mortality at 1 year, and a reduction in minor bleeding. (J Am Coll Cardiol 2005;45:1932–8) © 2005 by the American College of Cardiology Foundation

Diabetic patients are more prone to developing atherosclerosis (1) and generally have a worse long-term outcome after percutaneous coronary intervention (PCI) compared with non-diabetic patients. Previous studies have suggested that platelet glycoprotein (GP) IIb/IIIa inhibitors have an enhanced benefit in diabetic patients undergoing PCI (2) for acute coronary syndromes. A retrospective pooled analysis from three trials of abciximab had shown that use of abciximab may be associated with a one-year survival advantage among diabetic patients (3).

Based on this line of evidence, the use of GP IIb/IIIa inhibitors has been strongly advocated for diabetic patients undergoing PCI. The GP IIb/IIIa inhibitors, although useful for reducing peri-procedural events, are associated with an increased hazard of bleeding. Recently the Randomized Evaluation in PCI Linking Angiomax to Reduced Clinical Events (REPLACE)-2 study showed that bivalirudin with provisional GP IIb/IIIa inhibition is not inferior to heparin plus GP IIb/IIIa inhibition in patients undergoing elective or urgent PCI (4).Given the benefits of GP IIb/IIIa inhibitors in diabetic patients, however, it is important to confirm that the efficacy and safety of PCI in this population are not compromised by a bivalirudin-based antithrombotic strategy in which GP IIb/IIIa inhibitors are used only selectively.

Therefore, we evaluated the subgroup of diabetic patients enrolled in the REPLACE-2 trial to assess whether there

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Abbreviations and Acronyms

GP = glycoprotein
PCI = percutaneous coronary intervention
REPLACE-2 = Randomized Evaluation in Percutaneous Coronary Intervention Linking Angiomax to Reduced Clinical Events trial

was a difference in the short- or long-term outcome with the use of the two anticoagulation strategies. Further, we compared the outcomes of diabetic and non-diabetic patients to assess whether advances in medical care have ameliorated the high-risk profile associated with diabetes after percutaneous coronary revascularization.

METHODS

The design and results of the REPLACE-2 trial have been previously published (4). This trial randomized 6,010 patients undergoing elective or urgent PCI to either bivalirudin (0.75 mg/kg bolus and 1.75 mg/kg/h infusion) and provisional GP IIb/IIIa inhibitor or to heparin (65 U/kg bolus) and planned GP IIb/IIIa inhibition in a double-blind fashion. All patients received aspirin. Clopidogrel pretreatment was strongly encouraged, and all patients were treated with aspirin and clopidogrel for 30 days after PCI. Provisional GP IIb/IIIa inhibition (with an agent selected by the operator before the procedure or placebo if the patient was in the heparin and routine GP IIb/IIIa inhibitor arm) could be provided during the PCI at any time at the discretion of the operator for abrupt closure, flow-limiting dissection, side-branch closure, distal embolization, slow flow, or any other clinical or angiographic instability.

The primary end point was the composite of death, myocardial infarction, ischemia requiring urgent revascularization, or in-hospital major bleeding within 30 days. Myocardial infarction was centrally adjudicated by an independent panel and was defined as either: 1) creatine kinase or creatine kinase-myocardial band elevation $\geq$3 times the upper limit of normal if within two days of revascularization, or $\geq$2 times the upper limit of normal if not associated with revascularization; or 2) by new Q waves in two or more adjacent electrocardiographic leads. Major bleeding was considered to have occurred if any of the following definitions was satisfied: a hemoglobin decrease >4 g/dl; overt bleeding with hemoglobin decrease >3 g/dl; two or more units of blood transfused; or retroperitoneal, intraocular, or intracranial hemorrhage. Minor bleeding was defined as overt bleeding not meeting the criteria for major bleeding.

The trial excluded patients undergoing PCI as reperfusion therapy for acute myocardial infarction. Patients were also excluded if they required ongoing warfarin therapy or had been treated with unfractionated heparin within 6 h (unless the activated partial thromboplastin time was <50 s), low-molecular-weight heparin within 8 h, bivalirudin within 24 h, abciximab within 7 days, or eptifibatide or tirofiban within 12 h before randomization.

Diabetes was defined by patient report, the treating physician, or both. One-year follow-up was based on telephone contact and was obtained beyond 270 days in 98% of the cohort.

Statistical analysis. Baseline characteristics were summarized by the use of frequencies and percentages for categorical variables and means and standard deviation for continuous factors. Differences in baseline characteristics were tested with Pearson chi-square tests for categorical variables, Wilcoxon rank sum test for creatinine clearance, and activated clotting time and unpaired *t* test for age and weight. One-year event-free survival was illustrated with Kaplan-Meier curves, and outcomes were compared using the log-rank test. All analysis was intention to treat. A p value of < 0.05 was used as the level for statistical significance. The statistical software used was SAS version 8.0 (SAS Inc, Cary, North Carolina).

RESULTS

Diabetic status and outcome. The REPLACE-2 trial enrolled 1,624 diabetic patients and 4,368 non-diabetic patients (Table 1). The diabetic patients were more likely to be older, to have greater body weight, and to be female and minority patients. They were more likely to have had undergone prior coronary revascularization and to have hypertension or congestive heart failure. Conversely, they were less likely to be current or past smokers. Diabetic patients more frequently underwent multivessel and saphenous bypass graft interventions.

Table 2 describes the outcome of the entire population by diabetic status. Provisional therapy was used in 272 (6.2%) non-diabetic patients and 101 (6.2%) diabetic patients ($p = 0.99$). There was no difference in 30-day mortality between the two groups, whereas the incidence of myocardial infarction and urgent revascularization was greater in the non-diabetic population. Compared with non-diabetic patients, the diabetic patients were more likely to undergo target vessel revascularization by six months. At one year, there were 128 deaths in the entire cohort. Despite a seemingly better or equivalent early outcome, diabetic patients had an increased risk of death with significantly worse survival at six months and further separation of the survival curve by one year (Fig. 1).

Diabetic patients enrolled in the REPLACE-2 trial. Table 3 describes the characteristics of the diabetic patients randomized to the two treatment arms. There were no differences in any of the baseline demographic, clinical, or procedural characteristics between the two groups. Provisional GP IIb/IIIa inhibition was used in 36 (4.6%) patients randomized to the routine GP IIb/IIIa arm, compared with 65 (7.7%) patients in the bivalirudin arm ($p = 0.009$). Among these 65 patients, there was a high incidence of death (2, 3.1%), myocardial infarction (7, 10.8%), urgent

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Table 1. Baseline and Procedural Characteristics of the Patients Based on Diabetic Status

	Non-Diabetic Patients (4,368)	Diabetic Patients (1,624)	p Value
Age, yrs (mean ± SD)	62 ± 11	63 ± 10	<0.001
Age >75 yrs	571 (13.1%)	233 (14.3%)	0.19
Weight, kg (mean ± SD)	85 ± 17	93 ± 20	<0.001
Creatinine clearance, ml/min (mean ± SD)	93 ± 34	99 ± 43	0.06
Women	1,048 (24%)	484 (29.8%)	<0.001
Caucasian	4,102 (93.9%)	1,443 (88.9%)	<0.001
Prior MI	1,589 (36.9%)	593 (37.4%)	0.73
Prior PCI	1,469 (33.7%)	615 (38.2%)	0.001
Prior CABG	729 (16.7%)	370 (22.8%)	<0.001
Smoking within the last year	1,250 (29.3%)	304 (19.2%)	<0.001
Hypertension	2,687 (61.8%)	1,309 (80.8%)	<0.001
Congestive heart failure	232 (5.3%)	182 (11.3%)	<0.001
History of stroke	96 (2.2%)	45 (2.8%)	0.19
Procedure type			
Stent	3,734 (85.5%)	1,383 (85.2%)	0.75
Atherectomy	158 (3.6%)	69 (4.2%)	0.25
Balloon only	323 (7.4%)	123 (7.6%)	0.81
Multivessel intervention attempted	662 (15.4%)	285 (17.8)	0.03
Target vessel (not mutually exclusive)			
Left anterior descending	1,851 (42.4%)	652 (40.1%)	0.12
Left circumflex	1,198 (27.4)	507 (31.2%)	0.004
Right coronary artery	1,547 (35.4%)	537 (33.1%)	0.09
Left main	48 (1.1%)	24 (1.5%)	0.23
Bypass graft	233 (5.3%)	119 (7.3%)	0.004
Thienopyridine pretreatment	3,725 (85.3%)	1,426 (87.1%)	0.01
Median ACT, s (heparin + routine GP IIb/IIIa arm)	349	356	0.48

ACT = activated clotting time; CABG = coronary artery bypass graft; GP = glycoprotein; MI = myocardial infarction; PCI = percutaneous coronary intervention.

revascularization (2, 3.1%), and major bleeding (5, 7.7%). Figure 2 shows the early and long-term outcomes of the diabetic and non-diabetic patients enrolled in the two arms. Specifically, there was no difference in the incidence of early death, myocardial infarction, urgent revascularization, or any of the composite end points. There was no significant difference in the six-month incidence of target vessel revascularization in diabetic patients randomized to bivalirudin compared with those treated with GP IIb/IIIa inhibitors (101 [12.8%] vs. 77 [10.5%], p = 0.182). At one year, there was no significant difference in survival, with 19 (2.3%) deaths in the bivalirudin arm versus 30 (3.9%) deaths in the heparin and GP IIb/IIIa inhibitor arm (p = 0.065) (Fig. 3).

Bleeding outcomes. There was no difference in the incidence of major bleeding between diabetic and non-diabetic patients (3.1% vs. 3.3%, p = 0.76). There was a borderline significant interaction (p = 0.058) between diabetic patients and randomized treatment with respect to bleeding. Among

Table 2. Outcomes of Non-Diabetic Patients Compared With Diabetic Patients

	Non-Diabetic (n = 4,368)	Diabetic (n = 1,624)	p Value
Death at 30 days	13 (0.30%)	6 (0.37%)	0.66
MI at 30 days	305 (7.02%)	91 (5.62%)	0.05
Death/MI at 30 days	310 (7.12%)	91 (5.62%)	0.03
Urgent revascularization at 30 days	63 (1.45%)	16 (0.99%)	0.16
Urgent PCI at 30 days	37 (0.85%)	14 (0.86%)	0.96
Urgent CABG at 30 days	28 (0.64%)	2 (0.12%)	0.01
Death/MI/urgent revascularization at 30 days	344 (7.90%)	94 (5.80%)	0.005
Death at 6 months	43 (0.99%)	29 (1.79%)	0.012
Death/MI at 6 months	380 (8.81%)	131 (8.18%)	0.40
Target vessel revascularization at 6 months	346 (7.9%)	182 (11.2%)	<0.001
Death at 1 yr	79 (1.85%)	49 (3.06%)	0.004

Abbreviations as in Table 1.

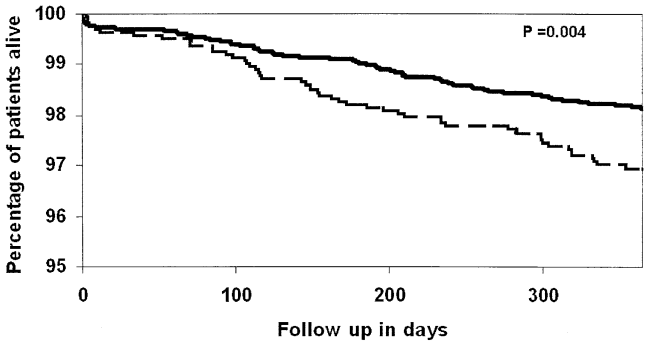

Figure 1. Survival of the cohort at one year based on diabetes status. **Solid line** = non-diabetic patients; **dashed line** = diabetic patients.

the diabetic patients, major bleeding was seen in 25 (3.0%) of patients randomized to the bivalirudin arm and 26 (3.3%) of those randomized to the GP IIb/IIIa inhibitor arm (p = 0.69), whereas among the non-diabetic patients, this occurred in 2.14% in the bivalirudin arm versus 4.42% in the GP IIb/IIIa inhibitor arm (p < 0.001). There was less minor bleeding in the bivalirudin arm in both diabetic (24.4% vs. 12.6%, p < 0.001) and non-diabetic (26.0% vs. 13.6%, p < 0.001) patients. The need for blood transfusion was low in both arms, with only 17 diabetic patients (2.2%) undergoing transfusion in the heparin and GP IIb/IIIa arm, compared with 20 (2.4%) in the bivalirudin arm (p = 0.77). Thrombocytopenia was less common in the bivalirudin arm (0.6% vs. 2.0%, p = 0.016)

DISCUSSION

Our data corroborate and extend findings from previous studies showing that compared with non-diabetic patients, diabetic patients have a similar short-term outcome after contemporary PCI but a markedly exaggerated long-term mortality risk. In the REPLACE-2 trial, compared with non-diabetic patients the diabetic cohort had no difference in early outcome, whereas the one-year mortality was significantly elevated. However, in parallel with the main trial, among the diabetic patients, there was no difference in

Table 3. Baseline and Procedural Characteristics of the Diabetic Patients Based on the Randomization Arm

	Heparin + Platelet GP IIb/IIIa Inhibitor (n = 784)	Bivalirudin (n = 840)	p Value
Age, yrs (mean ± SD)	64 ± 10	64 ± 10	0.61
Age >75 yrs	121 (15.4%)	112 (13.3%)	0.23
Weight, kg (mean ± SD)	93 ± 20	93 ± 20	0.75
Creatinine clearance, ml/min (mean ± SD)	98 ± 43	100 ± 43	0.13
Women	241 (30.7%)	243 (28.9%)	0.43
Caucasian	700 (89.3%)	743 (88.5%)	0.59
Anti-diabetes treatment			0.54
Diet only	94 (12.0%)	78 (9.3%)	
Thiazolidinedione	31 (4.0%)	39 (4.6%)	
Sulfonylurea/metformin	364 (46.4%)	385 (45.8%)	
Sulfonylurea/metformin + thiazolidinedione	48 (6.1%)	65 (7.7%)	
Insulin	118 (15.1%)	121 (14.4%)	
Insulin + oral	88 (11.2%)	104 (12.4%)	
Others	41 (5.3%)	48 (5.7%)	
Prior MI	283 (36.9%)	310 (37.9%)	0.67
Prior PCI	289 (37.1%)	326 (39.1%)	0.41
Prior CABG	181 (23.1%)	189 (22.65)	0.79
Smoking within the last year	147 (19.2%)	157 (19.1%)	0.96
Hypertension	643 (82.0%)	666 (79.6%)	0.21
Congestive heart failure	86 (11.1%)	96 (11.6%)	0.76
History of stroke	19 (2.4%)	26 (3.1%)	0.41
Procedure type			
Stent	675 (86.15)	708 (84.3%)	0.31
Atherectomy	31 (4.1)	38 (4.5%)	0.57
Balloon only	57 (7.3%)	66 (7.9%)	0.66
Multivessel intervention attempted	128 (16.6%)	157 (19.0%)	0.21
Target vessel (not mutually exclusive)			
Left anterior descending	312 (39.8%)	340 (40.5%)	0.78
Left circumflex	245 (31.3%)	262 (31.2%)	0.98
Right coronary artery	256 (32.7%)	281 (33.5%)	0.73
Left main	13 (1.7%)	11 (1.3%)	0.56
Bypass graft	55 (7.0%)	64 (7.6%)	0.64
Thienopyridine pretreatment	685 (87.5%)	741 (88.3%)	0.61

Abbreviations as in Table 1.

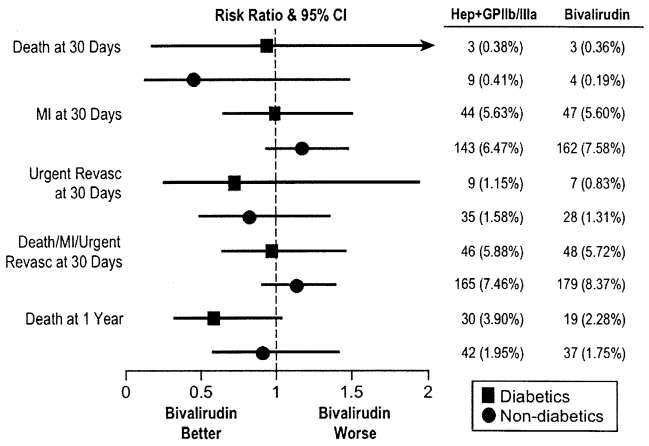

Figure 2. Outcomes of diabetic and non-diabetic patients by randomization arm. CI = confidence interval; GP = glycoprotein; Hep = heparin; MI = myocardial infarction.

ischemic events, need for revascularization, or one-year survival among those randomized to receive bivalirudin and provisional GP IIb/IIIa inhibitor versus those randomized to heparin and routine GP IIb/IIIa inhibitor.

Multiple studies have shown a worse outcome among diabetic patients after myocardial infarction (5), unstable angina (6,7), and coronary bypass grafting (8–10). Diabetic patients undergoing PCI seem to have a similar short-term outcome compared with non-diabetic patients, but have an increased risk of subsequent myocardial infarction, restenosis, and mortality (11). Indeed the Bypass Angioplasty Revascularization Investigation (BARI) trial showed better survival in patients randomized to coronary artery bypass grafting compared with those undergoing PCI (12). These findings were, however, not replicated in the BARI trial registry (13) and other studies (10) suggesting that PCI may be a viable revascularization strategy in carefully selected diabetic patients.

Multiple studies have focused on the short- and long-term outcomes of PCI among diabetic patients treated using contemporary techniques. In a study of 689 patients undergoing multivessel stenting at a single center, although there was no difference in the incidence of in-hospital death or myocardial infarction, the risk of target lesion revascularization or long-term mortality was significantly higher in diabetic patients (11). Similarly, data from the National Heart, Lung, and Blood Institute Dynamic registry described an almost two-fold increase in the risk of long-term mortality among diabetic patients compared with non-diabetic patients (14). Retrospective analysis from other large clinical trials replicates these findings. In the Prevention of Restenosis With Tranilast and Its Outcomes (PRESTO) trial, compared with the 8,798 non-diabetic patients, diabetic patients (n = 2,694) were more likely to have worse clinical and angiographic characteristics, although this risk profile did not translate into any apparent increase in short-term complications (15). Diabetic patients were, however, more likely to have new lesions, to have progression of previous lesions, or to die by nine months (2.1% vs. 0.9%).

Against this backdrop, the role of platelet GP IIb/IIIa inhibitors among diabetic patients undergoing PCI has undergone much scrutiny after publication of the combined analysis of the three trials of abciximab (3). In that study of 1,262 diabetic patients, use of abciximab was associated with a reduction in mortality from 4.5% to 2.5% (p = 0.031). Furthermore, in the diabetic substudy of the Evaluation of Platelet IIb/IIIa Inhibitor for Stenting Trial (EPISTENT) at six months, abciximab therapy was associated with a reduction in target vessel revascularization or the composite of death and myocardial infarction (16). The effects of abciximab on restenosis, however, could not be confirmed among the overall cohort of patients in the Evaluation of ReoPro and Stenting to Eliminate Restenosis (ERASER) trial (17) nor among diabetic patients in the Diabetes Abciximab Stent Evaluation (DANTE) study (18). Further support for the survival advantage of GP IIb/IIIa inhibitors came from a meta-analysis of six large trials that showed a significant mortality reduction with use of intravenous GP IIb/IIIa among diabetic patients with acute coronary syndromes (2). Among the 1,279 diabetic patients undergoing PCI during index hospitalization, the mortality rate was reduced from 4.0% to 1.2% (p = 0.002) with the use of GP IIb/IIIa inhibitors. Based on these data, the use of GP IIb/IIIa inhibitors had been advocated in all diabetic patients undergoing PCI (19,20). Recently, this hypothesis was directly tested in the Is Abciximab a Superior Way to Eliminate Elevated Thrombotic Risk in Diabetics (ISAR-SWEET) study (21). Among the 701 diabetic patients undergoing elective PCI after pre-loading with clopidogrel, no difference in either peri-procedural death, myocardial infarction, or urgent revascularization or in the primary end point of death and myocardial infarction at one year (8.3% vs. 8.6%, p = 0.91) was noted among patients randomized to abciximab or placebo. Although the study has been criticized for being underpowered, it remains the only direct test of GP IIb/IIIa inhibitors in this population (22).

The REPLACE-2 trial showed the non-inferiority of a strategy of bivalirudin with provisional GP IIb/IIIa inhibitors when compared with heparin plus routine GP IIb/IIIa inhibitors in a broad spectrum of patients undergoing PCI.

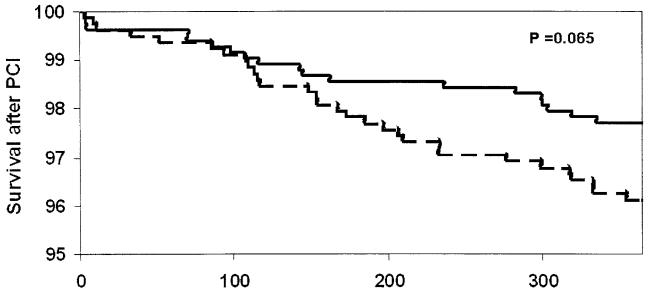

Figure 3. Survival of the diabetic patients by randomization arm. **Solid line** = bivalirudin; **dashed line** = glycoprotein IIb/IIIa inhibitor. PCI = percutaneous coronary intervention.

Given the apparent extraordinary benefit of GP IIb/IIIa blockade among diabetic patients, however, this subgroup deserves particular scrutiny. Our study provides reassuring data regarding the efficacy of the bivalirudin anticoagulant strategy among diabetic patients undergoing PCI. Not only was there no difference in short-term outcome among diabetic patients randomized to the two arms, but also the patients treated with bivalirudin had numerically better (although statistically non-significant) survival by 1-year follow-up. The number of patients in our analysis (n = 1,624) was similar to that in the prior analysis by Bhatt et al. (3) (n = 1,462) of abciximab, and the one-year mortality with the bivalirudin-based strategy (2.28%) or in the GP IIb/IIIa inhibitor arm (3.9%) is also comparable with that seen in their analysis (2.5% in the abciximab arm), or in the more contemporary Do Tirofiban and ReoPro Give Similar Efficacy Outcomes (TARGET) trial (2.1% in the tirofiban group and 2.9% in the abciximab group) (23). Although not definitive, the relatively large size of our cohort suggests that our findings are likely to be extant.

The biological basis of a long-term protective effect of a strategy of GP IIb/IIIa inhibition in diabetic patients has never been fully elucidated. Hypothesized mechanisms have included plaque stabilization, suppression of inflammatory mediators, reduced distal embolization, and an assuaged inflammatory response to vascular injury (24). Given that there are no data regarding whether bivalirudin as a direct thrombin inhibitor has these effects, the similar outcome with these two strategies cannot be fully explained. It is conceivable that parallel changes in interventional techniques, primary and secondary preventive measures, and improvements in clinical care that have occurred over the past decade may have diminished the additional long-term survival benefit of routine GP IIb/IIIa inhibition. However, it is equally plausible that a strategy of bivalirudin with provisional GP IIb/IIIa inhibition provides an analogous protective effect on the PCI site, thus explaining the similar survival in the two arms. However, these hypotheses have never been tested and need further investigation to support or refute them.

We did not find any reduction in major bleeding or the need for transfusion among diabetic patients treated with bivalirudin. This may relate to the small number of events and the lack of statistical power or may be a spurious finding given the relatively weak interaction in the setting of a secondary analysis. The incidence of major bleeding in the bivalirudin arm was similar among diabetic and non-diabetic patients, and was markedly higher among non-diabetic patients treated with GP IIb/IIIa inhibitors. Any conclusion from such data, however, needs to be made cautiously because such a protective interaction between diabetes and risk of bleeding with GP IIb/IIIa inhibitors has never been previously described.

Our results are based on a retrospective analysis of prospectively collected data and thus are prone to the limitations inherent to such studies. Further patients with ST-segment elevation myocardial infarction and non–ST-segment elevation myocardial infarction with ongoing ischemia were excluded from the REPLACE-2 trial and, therefore, our findings cannot be extended to this cohort. Data on glycemic control were not available. The small number of events combined with multiple anti-diabetes regimens prohibits a study of association of anti-diabetes therapy with short- or long-term end points. Our study was not powered to show either superiority or non-inferiority of one versus the other strategy in diabetic patients. However, given that the number of diabetic patients or events in our analysis is larger than in the previous analysis from the GP IIb/IIIa inhibitor trials, our data provide reassurance that the strategy of bivalirudin with provisional GP IIb/IIIa inhibitors does not carry any relevant mortality hazard. Given the reduction in bleeding events (albeit minor), shorter duration of infusion, and cost factors, it is likely that a large number of diabetic patients would be treated with bivalirudin and these data should serve to provide some evidence base for a clinician contemplating such a strategy.

CONCLUSIONS

Diabetes remains a major health care challenge, and there is a worse long-term survival rate among diabetic patients undergoing PCI. The strategy of using bivalirudin with provisional GP IIb/IIIa inhibition in diabetic patients is as effective as the combination of heparin plus routine GP IIb/IIIa blockade.

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